

What is claimed is:

1. A pharmaceutical composition comprising a gastrin compound having an extended activity upon administration to a subject in comparison with native gastrin.

2. A gastrin compound comprising: Z-Y<sub>m</sub>-X-AA<sub>1</sub>-AA<sub>2</sub>-AA<sub>3</sub>-AA<sub>4</sub>-AA<sub>5</sub>-AA<sub>6</sub>,  
5 wherein AA<sub>1</sub> is Tyr or Phe, AA<sub>2</sub> is Gly, Ala, or Ser, AA<sub>3</sub> is Trp, Val, or Ile, AA<sub>4</sub> is Met or Leu, AA<sub>5</sub> is Asp or Glu, and AA<sub>6</sub> is Phe or Tyr the AA<sub>6</sub> being amidated; wherein Z is a polymer which when the polymer is a protein, Z is the amino acid sequence of the protein; Y<sub>m</sub> is an optional spacer region comprising m amino acid residues of a small neutral amino acid, and X is selected from any consecutive portions of: residues 1-28 of  
10 SEQ ID NO: 1, residues 1-28 of SEQ ID NO: 2, residues 1-11 of SEQ ID NO: 3, and residues 1-11 of SEQ ID NO: 4, providing that the gastrin compound binds a gastrin/CCK receptor.

3. The gastrin compound according to claim 2, wherein AA<sub>1</sub>-AA<sub>2</sub>-AA<sub>3</sub>-AA<sub>4</sub>-AA<sub>5</sub>-AA<sub>6</sub> is Tyr-Gly-Trp-Met-Asp-Phe.

4. The gastrin compound according to claim 2, wherein AA<sub>1</sub>-AA<sub>2</sub>-AA<sub>3</sub>-AA<sub>4</sub>-AA<sub>5</sub>-AA<sub>6</sub> is Tyr-Gly-Trp-Leu-Asp-Phe.

5. The gastrin compound according to claim 2, wherein Z is a protein.

6. The gastrin compound according to claim 5, wherein Z is human serum albumin.

7. The gastrin compound according to claim 2, wherein Y is a sequence comprising  
20 m residues having glycine alternating with alanine or having a random sequence of glycine and alanine.

8. The gastrin compound according to claim 2, wherein X is selected from the group of sequences: position 1 to position 11 of SEQ ID NO: 3; position 1 to position 11 of SEQ ID NO: 4; position 2 to position 11 of SEQ ID NO: 3; and position 2 to  
25 position 11 of SEQ ID NO: 4.

9. The gastrin compound according to claim 2, further comprising a cysteine residue at the amino terminus of Y when m is greater than 1, or at the amino terminus of X when m is 0.

10. The gastrin compound according to claim 2, wherein m is 0 to about 20 residues.

11. The gastrin compound according to claim 2, wherein  $X_n-AA_1-AA_2-AA_3-AA_4-AA_5-AA_6$  further comprises a bifunctional cross-linking agent for linkage to Z if m is 0.
12. The gastrin compound according to claim 2 which is recombinantly produced.
- 5 13. A nucleotide sequence encoding the gastrin compound according to claim 2.
14. A cell carrying the nucleotide sequence according to claim 13.
15. The cell according to claim 14 which is a bacterial or a yeast cell.
16. The bacterial cell according to claim 15 which is selected from the group consisting of an *Escherichia*, a *Bacillus*, and a *Streptomyces*.
- 10 17. The yeast cell according to claim 15 which is selected from the group consisting of a *Saccharomyces*, a *Kluyveromyces*, a *Schizosaccharomyces* and a *Pichia*.
18. The gastrin compound according to claim 1 wherein the gastrin component contains at least amino acids selected from the group of: positions 29-34 of SEQ ID NO:1; positions 29-34 of SEQ ID NO:2; positions 12-17 of SEQ ID NO: 3; and positions 12-17 of SEQ ID NO: 4, and the gastrin is further associated with a protein, a polymer, a lipid or a carbohydrate.
- 15 19. The gastrin compound according to either of claims 2 or 18, wherein the gastrin component contains at least amino acids at positions 29-34 of SEQ ID NO:2 or positions 12-17 of SEQ ID NO:4.
- 20 20. The gastrin compound according to claim 18, wherein the polymer is a polyethylene glycol (PEG) or a dextran.
21. The gastrin compound according to claim 18, wherein the protein is a serum albumin.
22. The gastrin compound according to claim 21, wherein the serum albumin is human serum albumin.
- 25 23. A gastrin compound comprising a structure  $C-Y_m-X$ , wherein C is Cys or Lys,  $Y_m$  is an optional spacer region comprising m amino acid residues of a small neutral amino acid, and X is at least six amino acid residues comprising sequences selected from at least positions 12-17 of gastrin-17 (SEQ ID NO: 3 and 4) and at least positions 29-34 of gastrin-34 (SEQ ID NO: 1 and 2).
- 30 24. The gastrin compound according to claim 23, further conjugated to a polymer.

25. The gastrin compound according to claim 23, further conjugated to a polyethylene glycol (PEG) or a dextran.
26. The gastrin compound according to claim 23, further conjugated to a protein.
27. The gastrin compound according to claim 23, further comprising a bifunctional cross-linking agent wherein a first reactive end of the cross-linking agent is covalently linked to C.
28. The gastrin compound according to claim 23, wherein a second reactive end of the cross-linking agent is covalently linked to a polymer or protein.
29. The gastrin compound according to claim 23, wherein C-Y<sub>m</sub>-X is produced recombinantly or is synthesized by peptide synthesis.
30. The gastrin compound according to any of claims 1, 2 and 23, in an effective dose.
31. The gastrin compound according to any of claims 1, 2 and 23, further comprising an agent for immune suppression.
32. The gastrin compound according to any of claims 1, 2 and 23, further comprising a growth factor.
33. The gastrin compound according to claim 32, wherein the growth factor is a glucagon-like peptide 1 receptor ligand.
34. The gastrin compound according to claim 32, wherein the growth factor is an EGF receptor ligand.
35. The gastrin compound according to claim 1, 2 and 23, further comprising a hypoglycemic agent.
36. The gastrin compound according to any of claims 1, 2 and 23, further comprising a pharmaceutically acceptable carrier.
37. A method of treating a subject having diabetes, comprising administering a gastrin compound according to any of claims 1, 2 and 23.
38. The method according to claim 37, wherein frequency of administering the gastrin compound is less than frequency of administration of a native gastrin.
39. The method according to claim 37, further comprising measuring a physiological indicator of islet neogenesis.

40. The method according to claim 37, further comprising measuring fasting blood glucose (FBG).
41. The method according to claim 37, further comprising decreasing insulin dependency.
- 5 42. A method of making a gastrin compound comprising associating an amino acid sequence of a gastrin with a carrier composition.
43. The method according to claim 42, wherein prior to associating the gastrin with the carrier, the gastrin is modified to comprise a cysteine substitution or an additional cysteine residue.
- 10 44. The method according to claim 43, wherein the cysteine substitution is a replacement of pyroglutamate.
45. The method according to claim 42, wherein the gastrin amino acid sequence comprises at least positions selected from the group of: residues 29-34 of amino acid sequence SEQ ID NO: 1; residues 29-34 of amino acid sequence SEQ ID
- 15 NO: 2; residues 12-17 of amino acid sequence SEQ ID NO: 3; and residues 12-17 of amino acid sequence SEQ ID NO: 4.
46. The method according to claim 43, wherein the cysteine is at the amino terminus of the gastrin.
47. The method according to claim 42, further comprising prior to associating the
- 20 gastrin with the carrier, modifying the gastrin to further comprise a bifunctional cross-linking agent.
48. A method of treating a diabetes patient comprising administering to the patient a modified gastrin capable of covalently reacting with a serum protein.
49. The method according to claim 48, wherein the modified gastrin comprises a
- 25 sequence of a native gastrin capable of binding to the gastrin/CCK receptor and an amino terminal cysteine or lysine.
50. The method according to claim 42, wherein the sequence of the native gastrin is selected from the group of: residues 29-34 of amino acid sequence SEQ ID NO: 1; residues 29-34 of amino acid sequence SEQ ID NO: 2; residues 12-17 of amino
- 30 acid sequence SEQ ID NO: 3; and residues 12-17 of amino acid sequence SEQ ID NO: 4.

51. A method for maintaining for an extended period of time an increased gastrin serum level compared with the serum level of a peptide having an amino acid sequence of a gastrin, the method comprising administering a gastrin compound according to any of claim 1, 2 and 23.
- 5 52. A kit comprising at least one effective dose of a gastrin compound according to any of claims 1, 2 and 23.
53. A gastrin compound according to Claim 9, further comprising a bifunctional crosslinking agent for linkage to Z.